REMARKS/ARGUMENTS

Claims 1-33 have been cancelled through previously submitted Amendment. Claim 34-51 are pending. No amendment is made to any of the pending claims. Reconsideration of the present application in view of the following remarks is respectfully solicited.

I. Rejection of claims 34-51 as being obvious under 35 U.S.C. §103(a) over Morris et al. (EP 0 830 858 A1) as evidenced by Nakajima et al. (U.S. 3,926,817)

Claims 34-51 stand rejected as being obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Applicants respectfully traverse.

Claim 34 recites a pharmaceutical formulation comprising a homogeneous mixture of: (a) **uncoated** olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; d) one or more additional excipients.

Morris teaches an olanzapine formulation in which the active ingredient olanzapine is coated by a polymer. Morris repeatedly emphasizes the criticality of coating olanzapine with a suitable polymer in many paragraphs. *See*, for example, the abstract, page 2, lines 6-28 and 45-51, page 4, lines 45-57, and claim 1. Morris does not disclose a formulation comprising uncoated olanzapine.

At page 3 of the Office Action, the Examiner states: "Morris teaches that uncoated olanzapine are well within the purview of the skilled artisan." The Examiner's statement is incorrect. To the contrary, Morris teaches away from the use of uncoated olanzapine in a tablet formulation.

As noted above, Morris consistently discloses and emphasizes in the abstract, specification, and the claims the criticality of coating olanzapine with a suitable polymer. As

evident from the full text of Morris, coated olanzapine is a necessary and essential feature of the invention described therein.

Contrary to the Examiner's statement, Morris in fact contains many statements that would discourage or teach away a person of ordinary skill in the art from making an uncoated olanzapine formulation. For example, at page 2, lines 6-13, Morris discloses,

> "However, improved oral formulations were desired in light of the moisture sensitive, metastable nature of olanzapine, the tendency of olanzapine to undesirably discolor in the known tablet formulation, that is the formulation disclosed in [U.S. Patent No.] 5,229,382, and due to the surprisingly potent nature of olanzapine. A pharmaceutically elegant granule or microparticle formulation was especially desired. Such granule formulation was particularly challenging in light of the exacerbating effect of surface contact with ambient air and moist environments and the relatively large surface area inherent in a granule formulation.

At page 2, lines 32-51, Morris discloses:

> Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.
>
> Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.
>
> Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.
>
> The discoloration phenomenon is particularly troublesome for a granule formulation. Such formulation inherently exposes more olanzapine to ambient or humid conditions by virtue of the increased outer surface area relative to a solid tablet formulation. The present invention provides the desired pharmaceutically elegant granule formulation.

> Applicants have discovered that coating the olanzapine compound with a polymer selected from . . . as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation.

When reading the above disclosures, a person of ordinary skill in the art would not leave olanzapine uncoated, which would result in undesirable color change and appearance, in particular considering that the olanzapine formulation would be used for a patient suffering from hallucinations, delusions, and being out of touch with reality. See MPEP 1504.03 ("A *prima facie* case of obviousness can be rebutted if the applicant...can show that the art in any material respect 'taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." *In re Haruna*, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001).

The Examiner appears to agree now that Morris fails to teach the use of an uncoated olanzapine in the oral formulation. *See* pages 5-6, the bridging paragraph of the Office Action. Nor does the Examiner negate that a person of ordinary skill in the art would not use an uncoated olanzapine in an oral formulation for normal use. Nevertheless, the Examiner continues to argue: "it would be within the skilled artisan [sic] to formulate the tablets as uncoated tablets if the intended use is for rapid usage of the formulation before the discoloration period and/or for rapid dissolution." *See* page 6, first full paragraph of the Office Action. For reasons expressed below, the Examiner's argument lacks merit.

First, assuming *arguendo* that there is a desire for an olanzapine that is rapidly consumed, a person of ordinary skill in the art would use a coated, not un-coated olanzapine in a tablet. As noted above, Morris teaches that discoloration occurs after the uncoated olanzapine tablets are

exposed to open air. If one would use uncoated olanzapine for rapid consumption, as suggested by the Examiner, s/he should at least warn physicians and patients that the uncoated olanzapine product should be consumed as soon as possible after the package is opened. In case that the package is opened and the product is not used up immediately, the unused product will have to be abandoned due to the occurrence of discoloring. Alternatively, one may consider placing only one unit dosage of tablet(s) in an amber, high density polyethylene bottles for one-time use, which will unduly increase the manufacturing cost and be unacceptable to a manufacturer. Also, because uncoated olanzapine is so sensitive to the open air, as taught in Morris, various precautions should be adopted to make sure that the uncoated olanzapine formulation is packaged well and tight, therefore resulting in increased cost.

Therefore, in view of these problems and difficulties associated with uncoated olanzapine, as suggested by Morris, a person of ordinary skill in the art would not use any uncoated olanzapine for any use, even for rapid consumption, as suggested by the Examiner, in particular considering the existence of other alternative, i.e., coated tablets. Specifically, because Morris taught that coated olanzapine tablets do not have any of the problems associated with uncoated olanzapine tablets, one would use coated olanzapine tablets for normal use or "rapid consumption" as proposed and speculated by the Examiner. *See* also MPEP 2145X. D.3 ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).")

Second, assuming arguendo one would attempt to use uncoated olanzapine tablets for rapid consumption, as suggested by the Examiner, this person would not have any reasonable expectation of success to do so. *See* MPEP 2143.02 ("Reasonable Expectation of Success Is

Required.") Specifically, at page 4, lines 45-45, Morris discloses: "Uncoated tablets stored at ambient conditions in amber, high density polyethylene bottles do not show signs of discoloration after 24 months; however, if the bottle is opened such that the tablets are exposed to open air then discoloration occurs **within** 5 days." (Emphasis added.") This statement plainly conveys that uncoated tablets will discolor **ANY** time, but by no later than 5 days, after the tablets are exposed to air. Therefore, there is possibility that the uncoated tablets may discolor as soon as they are exposed to the air, presumably depending on the condition and environment (such as humidity) under which the uncoated tablets are exposed. The Examiner appears to incorrectly understand that Morris teaches that uncoated olanzapine tablets would not discolor for an ascertained period of time, e.g., 5 days.

Moreover, **the unexpected results of the present invention further demonstrate the non-obviousness of the invention described in claim 34**. See MPEP 2141 (Secondary considerations, such as unexpected results, must be evaluated under 35 U.S.C. § 103.) Although Applicants have presented this argument previously, the Examiner fails to consider it as required by MPEP2141.

Specifically, as noted above, according to the statement quoted by the Examiner from page 4, lines 45-48 of Morris, a person of ordinary skill in the art would expect that a formulation containing uncoated olanzapine would discolor any time but by not later than 5 days after the tablets are exposed to air under room temperature and 40% relative humidity. In contrast, it is Applicants, not others, who surprisingly discovered that a tablet formulation comprising a homogeneous mixture of uncoated olanzapine and other excipients in accordance with the present invention. As explained at page 3, last paragraph of the present application,

> It was surprisingly found by the present inventors that stable pharmaceutical formulations comprising olanzapine as the active

> ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogeneously mixed with certain excipients and then subjected to direct compression. The direct compression is preferably performed in the absence of any solvent. In view of the fact that the excipients used by the present inventors are commonly used for manufacturing tablets, the finding that they allow the production of stable olanzapine formulations without any need for a coating or wet granulation was totally unexpected.

It is noted that at page 3, lines 10-13 of the Office Action, the Examiner states: "Given that Morris teaches the exact same ingredients as applicant, the Examiner thereof contends that no such discoloration would occur if one of ordinary skill in the art opts to utilize the uncoated olanzapine along with the specific excipients discussed by Morris." The conclusion is apparently drawn from the hindsight review of the present application, not Morris or any other art of record. As explained above, nowhere does Morris teach the use of uncoated olanzapine tablets, let alone any benefit of doing so. As instructed by MPEP 2142, "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art."

Additionally, the Examiner has previously stated that the findings by WIPO do not necessarily bind on USPTO's examination of the counterpart application. While Applicants do not argue that USPTO should be necessarily bound by WIPO's decision, Applicants would like again bring the Examiner's attention to the underlying substantive reasons for WIPO's findings that the claims of the corresponding PCT application are novel and have an inventive step in view of the same prior art applied by the Examiner here, i.e., Morris et al. For example, **WIPO's specific discussion** as to why the claims are novel and have an inventive step in view of Morris certainly **sheds light on how a person of ordinary skill in the art would understand Morris, the differences between Morris and the present invention, and whether the results of the**

present invention would be unexpected from Morris. Indeed, WIPO's understanding about Morris is consistent with Applicants' above statement that Morris fails to teach a formulation comprising uncoated olanzapine and in fact teaches away from such a formulation.

Based on the foregoing, claims 34 is not obvious over under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. For at least the same reasons, none of claims 35-51, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Withdrawal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima is respectfully requested.

II. Rejection of claims 34-51 as being obvious under 35 U.S.C. §103(a) over Chakrabarti et al. (U.S. 5,229,382) in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321).

Claims 34-51 are newly rejected as being unpatentable over Chakrabarti et al. in view of Rubinstein et al. under under 35 U.S.C. §103(a). Applicants respectfully traverse.

EP054436B1, the European counterpart to Chakrabarti et al. (a U.S. patent), has been extensively discussed in the present application. *See* pages 1-2, the bridging paragraph and pages 2-3, the bridging paragraph.

While the Examiner acknowledges some deficiencies of Chakrabarti et al., the Examiner fails to recognize that Chakrabarti et al. fail to disclose a **homogeneous mixture** of: (a) uncoated olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; and d) one or more additional excipients, as recited in independent claim 34 of the present application. Chakrabarti et al. merely teach a formulation prepared by granulation and compression. See Example 4 of Chakrabarti et al.

Chakrabarti's method of granulating does not lead to a homogenous mixture of

olanzapine with other excipients as not every excipient and the active ingredient are dissolved in the granulation liquid. If some are dissolved and the granulation liquid is then sprayed onto other excipients/active ingredient, the result are granules with a core of the non-dissolved excipients/active ingredient, covered with a layer of previously dissolved excipients from the granulation liquid.

The secondary reference Rubinstein et al discloses general methods of preparing compressed tablets, and cannot remedy the deficiency discussed above in connection with the primary reference Chakrabarti et al. Therefore, combination of Chakrabarti et al. and Rubinstein et al., as proposed by the Examiner, would not lead to the formulation of claim 34. Therefore, claim 34 is not obvious over under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein et al. For at least the same reason, none of claims 35-51, each of which depends from claim 34, is obvious over under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein et al. Withdrawal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein et al. is respectfully requested.

Based on the foregoing, it is believed that the present application has been placed in condition of allowance. Early and favorable consideration is respectfully requested.

It is believed that no additional fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN PONTANI LIEBERMAN & PAVANE LLP

By /Kent H. Cheng/
Kent H. Cheng
Reg. No. 33,849
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

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